REMARKS

The finality of the Restriction Requirement has been noted.

Claims 1-2, 4-29, 32-34 and 36-72 were rejected under 35 U.S.C.§112, first paragraph.

Reconsideration is requested.

The Examiner objected to the use of the term "consisting essentially of" in the claims, I response the claims have been amended to insert the term "comprises" which is supported by the original claims.

For this reason, it is requested that this ground of rejection be withdrawn.

Claims 1, 4-5, 8-11, 14-29 and 32-33, 36-37, 40-60, 62-65, 68-69 and 71-72 were rejected under 35 U.S.C.§103(a) as being unpatentable over Glassman in view of Paradisssis et al. (Paradissis) and Webb et al. (Webb)..

Reconsideration is requested.

A key feature of the present invention is that it results in the reduction in the size of the claimed dosage form which is a high dose of a highly soluble active ingredient. This result is not made obvious by the prior art but made possible by the claimed dual retard technique.

The dose of a particular high dose, highly soluble active ingredient will differ from other high dose, highly soluble active ingredients and hence it is not practical to recite dimensions for the claimed dosage form. The size of the controlled release dosage form of high dose, highly solubility active ingredient in the instant invention is mainly dependent on amount of release controlling agent and the dual retard technique used to control the drug release. Hence, the ratios between high dose, high solubility active ingredient, micromatrix particles and hydrophobic release controlling agent are recited in the amended claims in order to point out the invention.

The advantage of being able to make a smaller dosage form flows from the structure that is recited in the amended claims.

The Glassman patent discloses double layer tablets wherein the outer layer preferably contains pure active ingredient. This inner portion is separated immediately on contact with GI fluid to provide super fast release of drug and the second tightly compressed layer disintegrates slowly and provides sustained or delayed release action. Glassman teaches that by adding a bicarbonate salt to the top layer, quicker dissolution of the top layer may be achieved. Moreover, both the layers are essentially connected by a middle layer (Fig 2, layer 18) of talc or corn starch for cementing the layers together and in addition, the middle layer may also contain an effervescent combination for rapid release of the outer layer. Glassman is silent as to the relative size of the dosage form or the ratio between drugs and release controlling agents.

An objective of this invention is to reduce the latent period particularly that is seen in the case of slow acting compositions where immediate therapeutic action followed by sustained effect is essential in the treatment of conditions such as asthma, angina etc.

Claims 1 and 33 have been amended to recite the ratios between high dose, high solubility active ingredient, micromatrix particles and hydrophobic release controlling agent in addition to the feature that the inner portion is covered by the outer portion from all the sides except a top surface that remains uncovered.

Glassman discloses a sustained / delayed release action that is obtained using enteric coating and does not teach the use of hydrophobic release controlling agents. In addition this prior art reference clearly mentions the use of single drug formulation having immediate and sustained release profiles to achieve instant action and sustained action. It does not describe a tablet where a structure is

embedded in a tablet and only the top surface remains uncovered as pointed out in claims 1 and 33. For this reason, Glassman does not teach the controlled release dosage formulation that is defined by amended claim 1.

Paradissis only discloses an extended release pharmaceutical composition particularly adapted to approach zero order drug release over a period of 12 - 24 hours. The release of the drug in the present invention is controlled through diffusion. It discloses a mixture of an immediate release particles containing a core of drug, inert spherical substrate particles and a binder, coated with talc. The talc, which is an essential ingredient, is employed to prevent the drug layer from interfering with film formation on the particles and to prevent drug migration during storage (col. 6, line 5-12). The formulation essentially comprises particles of -10 to + 60 mesh size, as being necessary to achieve the desired release of the drug (col. 3 line 30-33 and claim 1).

It has been found by the inventors of the present application that when the difference between the dosage strengths of two components is very high and particularly in the case of high solubility drugs, it is difficult to formulate a dosage form that will provide a sustained release profile. The amended claims of the present application point out a combination of a high dose-highly soluble active ingredient of a controlled release dosage form in combination with a low dose active drug as the immediate release component. This significantly reduces the amount of inactive components and thereby reduces the size of the dosage form for ease of swallowing and economy.

There is no suggestion or teaching in either Glassman or Paradissis that would lead a skilled artisan to the claimed invention. The prior art does not teach the specific ratios of claims 1 and 33 would lead to the desired controlled release pattern for a highly soluble drug and at

the same time would permit the making of a smaller more compact dosage form.

Webb discloses a compressed tablet having discrete zones which are made from a formulation (A) having a sustained release profile and contains a active ingredient particularly a sympathomimetic agent. A water soluble non-ionic cellulose ether is used in an amount from about 18% to 50 % by wt of formulation A, one or more anionic surfactants in an amount from about 2% to 20 % by wt of formulation A with other pharmaceutically acceptable excipients and formulation (B) having immediate release profile containing drug, calcium carbonate in an amount from about 0.5% to 25% by wt of formulation B, nonionic surfactants in an amount from about 1% to 10 % by wt of formulation B. Compression is applied by any suitable technique.

The Examiner has acknowledged that neither Paradissis or Glassman suggest an inlaid tablet structure where only one of six sides of an discrete section are exposed to the outer surface of the tablet. Webb is limited to a formulation for sympathomimetic agents and essentially requires surfactants and calcium carbonate. There is no motivation to use the teaching from Webb to prepare an inlay dosage form based on a tablet having a high dose-high solubility active ingredient and a low dose active ingredient as an immediate release active ingredient. For these reasons, it is requested that this ground of rejection be withdrawn.

Claims 6-7 and 12-13, 36 - 39 and 44 - 45 were rejected under 35 U.S.C.§103(a) as being unpatentable over Glassman in view of Paradissis, Webb and Lerner et al. (Lerner).

Reconsideration is requested.

The Glassman, Paradissis & Webb references have been distinguished from claim 1 and claim 33 above. Lerner describes gastrointestinal drug delivery systems for delivery of enterally administered compositions to specific

locations along the GI tract. In particular, the colon is targeted as a release site. The Lerner invention is directed to a composition comprising a core and coating wherein the core contains drug with carrier material, which preferably swells in contact with GI fluid. Lerner teaches that the formulation operates by allowing the slow introduction of fluid into the device, which swells the particulate matter and the particles eventually form channels from the outer part of the device to the core containing the drug and the drug can than be released from the channels. This formulation controls the release of the drug at a particular site of absorption based on the various parameters such as thickness of the outer coating (essentially contains rate controlling agents), the amount of particulate embedded in the coating, the type of particulate embedded in the coating, the particle size distribution of the particulate embedded in the coating and the core carrier. Thus Lerner is limited to the disclosure of a delivery device for site specific delivery of drug and having drug release through osmotic channels and the release is controlled by a combination of hydrophilic particulate and hydrophobic component (col. 20 line 36- col. 21 line 47). This patent does not teach the dual retard technique for combination of immediate release and sustained release formulations without the use of hydrophilic particulate matter. For these reasons, this combination of references fails to make claims 1, 6-7 , 12-13 and 36-37 obvious and it is requested that this ground of rejection be withdrawn.

None of the prior art teaches such a techniques for high dose high solubility drugs, which reduces burst effect and also reduces the size of the dosage form. For these reasons, it is requested that this ground of rejection be withdrawn.

It is respectfully submitted that nobody would disagree with the argument of Examiner that all the components of instant invention are individually present in

the cited prior art. However, the combination defined by the claims cannot be derived from the prior art by picking an choosing the elements according to the present application.

The prior art does not disclose in any way the disclosed objective of the instant invention which is to provide a dosage formulation for **high dose, high solubility active ingredients in sustained release form along with low dose active ingredients as immediate release form to the extent that it achieves a desired therapeutic release profile.** These aspects were not taught by any of the prior art individually as well as taken together.

For these reasons, it is requested that this ground of rejection be withdrawn.

An early and favorable action is earnestly solicited.

Respectfully submitted,

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